Hereditary Tyrosinemia

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Austin Larson

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A. Larson (✉)
Clinical Genetics and Metabolism, Children's Hospital Colorado, University of Colorado Denver – Anschutz Medical Campus, Aurora, CO, USA
e-mail: Austin.Larson@childrenscolorado.org

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Core Messages

- Tyrosinemia type 1 causes liver failure, liver cancer, renal tubular dysfunction, and recurrent episodes of peripheral neuropathy when untreated, resulting in significantly shortened life expectancy.
- Treatment with NTBC prevents the severe manifestations of disease but results in hypertyrosinemia.
- Dietary treatment of tyrosinemia type 1 with limitation of phenylalanine and tyrosine intake is indicated to prevent severe hypertyrosinemia and the associated complications in patients treated with NTBC as well as in those with type 2.

13.1 Background

Disorders resulting from enzyme deficiencies in the tyrosine catabolism pathway have widely variable phenotypes depending on the specific location of the enzymatic block in the pathway and the resultant perturbation of biochemistry. This chapter will focus primarily on tyrosinemia type 1, including both the treated and untreated phenotypes, and will also discuss tyrosinemias type 2 and 3. Other disorders of tyrosine catabolism such as alkaptonuria and hawkinsinuria will not be addressed.

13.2 Biochemistry

Tyrosinemia type 1 is caused by a deficiency in fumarylacetoacetate hydrolase (FAH), which is the final step in the phenylalanine/tyrosine catabolic pathway (Fig. 13.1). The enzyme deficiency results in the accumulation of fumarylacetoacetate, maleylacetoacetate, succinylacetoacetate and succinylacetone. The accumulation of these molecules results in direct toxicity to cells in the liver and kidneys [1]. Additionally, succinylacetone is an inhibitor of porphobilinogen synthase, which can result in both a biochemical and clinical phenocopy of an acute porphyria neurological crisis due to accumulation of neurotoxic heme

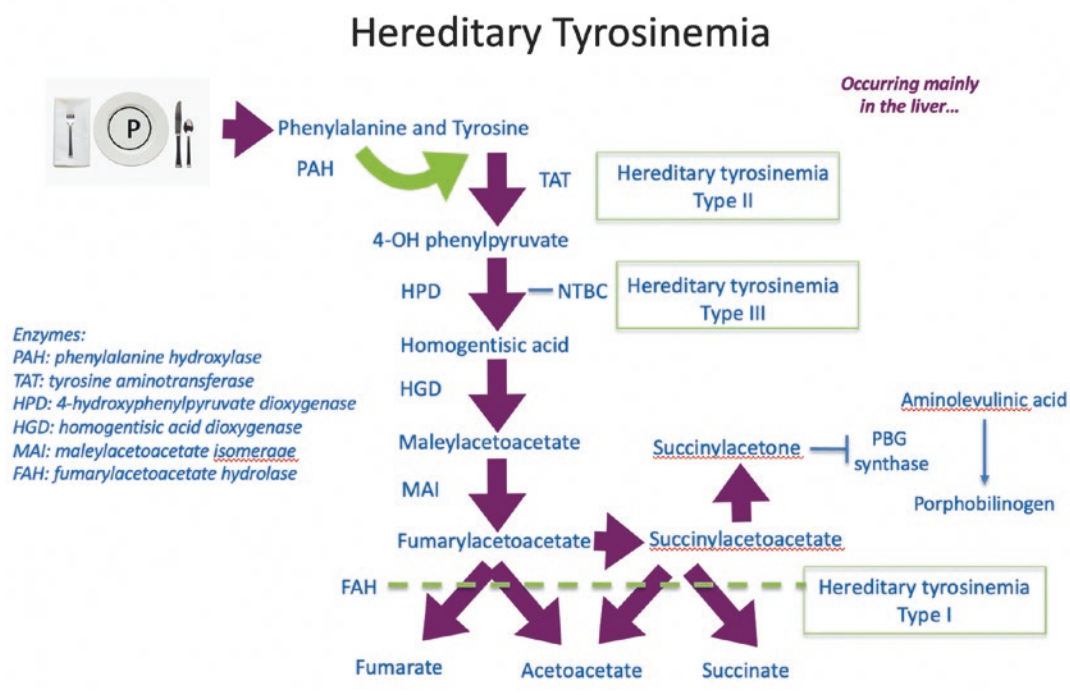

Fig. 13.1 Hereditary tyrosinemia. Enzymes: PAH phenylalanine hydroxylase, TAT tyrosine aminotransferase, HPD 4-hdroxyphenylpyruvate dioxygenase, HGD homogentisic acid dioxygenase, MAI maleylacetoacetate isomeraae, FAH fumarylacetaacetate hydrolase

precursors in some patients [2]. Despite the name, tyrosinemia type 1 does not typically result in clinically significant elevations in tyrosine because the causative enzyme block is several reactions removed from tyrosine, though there may be mildly elevated tyrosine concentrations as a secondary phenomenon.

In contrast, tyrosinemia type 2 (tyrosine aminotransferase (TAT) deficiency) and tyrosinemia type 3 (4-hydroxyphenylpyruvate dioxygenase (HPD) deficiency) do cause significant tyrosine elevations since these two reactions are more proximal in the tyrosine catabolism pathway. Unlike untreated tyrosinemia type 1, the toxic metabolite responsible for most of the manifestations of tyrosinemias type 2 and 3 is tyrosine itself.

13.3 Diagnosis

Tyrosinemia type 1 is on the Recommended Uniform Screening Panel and is now typically diagnosed via newborn screening. Succinylacetone and tyrosine are both detectable in dried blood spot samples. Succinylacetone is a much more sensitive and specific diagnostic metabolite for tyrosinemia type 1 than tyrosine and is the preferred test [3]. Until recent years, many U.S. states did not assess succinylacetone concentration as part of NBS and as a result, many patients were diagnosed only after the development of symptoms. Succinylacetone has been used as a diagnostic metabolite on NBS in Quebec for much longer than in other regions because the prevalence of tyrosinemia type 1 is much higher due to the prevalence of an *FAH* variant (c.1065 + 5 G > A) in the population [4]. Much of the initial literature highlighting the differences in natural history between presymptomatic diagnosis and treatment versus ascertainment only of symptomatic patients is derived from the experience in Quebec.

Tyrosinemias type 2 and 3 are considered secondary conditions for NBS. Tyrosine itself is the diagnostic metabolite for identification of risk for these two conditions on NBS. However, significantly elevated tyrosine may have other etiologies as well. Transient tyrosinemia is a relatively common and benign condition that has increased prevalence in premature infants and typically resolves without intervention in the first few months of life. Tyrosine may also be elevated in those with liver disease of any etiology [5]. When liver disease is the etiology of elevated tyrosine, methionine and phenylalanine are often also elevated concurrently.

All the tyrosinemias are autosomal recessive conditions and molecular genetic testing demonstrating biallelic pathogenic (or likely pathogenic) variants can confirm a suspected diagnosis based on biochemical and clinical features. Tyrosinemia type 1 is caused by biallelic variants in *FAH,* type 2 by variants in *TAT* and type 3 by variants in *HPD*.

Repeatedly elevated measurements of succinylacetone in blood should be considered a presumed diagnosis of tyrosinemia type 1 and treated accordingly even prior to confirmatory testing. Succinylacetone measurement in blood is preferred to measurement in urine due to increased sensitivity [6].

13.4 Clinical Presentation and Natural History

Most individuals with tyrosinemia type 1 who are not diagnosed and treated presymptomatically will develop liver disease in the first year of life. There may be acute liver failure requiring liver transplantation or chronic hepatopathy. The acute liver failure may be fatal if not successfully managed with liver transplantation. Hepatocellular carcinoma is common in untreated tyrosinemia type 1, with a peak incidence at age 4–5 years and is a frequent cause of death in untreated tyrosinemia type 1 [7]. Significantly elevated alpha-fetoprotein is a nonspecific biomarker of tyrosinemia-associated hepatopathy. It is important to interpret alpha-fetoprotein concentrations using expected values for age since the normal concentrations of alpha-fetoprotein change by orders of magnitude over the first months of life [8].

The patients that do not have symptoms of hepatopathy as their primary manifestation may come to clinical attention due to renal disease. These individuals likely have some residual FAH enzyme activity resulting in slower progression

of disease. Renal tubular dysfunction results in acidosis and phosphate wasting. The renal tubular acidosis contributes to growth restriction. Hypophosphatemia leads to rickets, which also causes decreased linear growth. Urine studies for patients with renal manifestations of tyrosinemia type 1 include generalized aminoaciduria and impaired tubular resorption of phosphorus [9].

About 40% of individuals with tyrosinemia type 1 develop neurological crises that are often recurrent. The pathogenesis of the neurological symptoms is the same as in acute intermittent porphyria and results from the inhibition of porphobilinogen synthase by succinylacetone. The resultant lack of flux through the heme synthesis pathway results in accumulation of heme precursors that are toxic to both the central and peripheral nervous system. Patients with tyrosinemia-related neurological crises develop acute-onset neuropathy resulting in hypotonia, gastrointestinal dysmotility and weakness that may affect the diaphragm and require intubation and mechanical ventilation [10]. The neurological crises may be fatal in some patients.

Tyrosinemia type 2 is associated with keratopathy, manifesting as photophobia, lacrimation, and ulceration of the cornea. These symptoms are a direct manifestation of hypertyrosinemia and are largely reversible if tyrosine levels are decreased with treatment [11]. Hyperkeratosis and blistering of the palms and soles are also associated with hypertyrosinemia. Individuals with both types 2 and 3 tyrosinemia have increased prevalence of developmental delay and intellectual disability, which may be a direct effect of increased tyrosine in the brain interfering with neurotransmitter metabolism [12].

13.5 Pharmaceutical Treatment of Tyrosinemia Type 1

Prior to the advent of pharmaceutical therapy, physicians had determined that dietary restriction of phenylalanine and tyrosine did not sufficiently decrease the production of toxic metabolites for patients with tyrosinemia type 1 to alter the natural history of the disease. Treatment consisted of close monitoring for hepatopathy, hepatocellular carcinoma or neurological crises and then liver transplantation upon occurrence of one or more of those outcomes. Liver transplantation significantly reduces but does not eliminate the production of succinylacetone. Patients that underwent liver transplantation for tyrosinemia type 1 had 90% 5-year survival and did not have recurrence of hepatocellular carcinoma in the graft [13]. Despite liver transplantation, there may be some ongoing risk of renal disease related to ongoing low-level production of succinylacetone [14].

The discovery that 2-(2-nitro-4-trifluoromethylbenzyol)-1,3 cyclohexanedione (NTBC), also known as nitisinone, inhibits 4-hydroxyphenylpyruvate dioxygenase led to its development as a treatment for tyrosinemia type 1 and it was approved by regulatory agencies for that indication in the early 1990s [15]. By blocking flux through the tyrosine catabolism pathway at a more proximal step, NTBC treatment prevents the accumulation of fumarylacetoacetate and succinylacetone [16]. The natural history of tyrosinemia type 1 has changed dramatically due to pre-symptomatic diagnosis and treatment with NTBC. Patients that maintain therapeutic concentrations of NTBC and sufficiently block the production of succinylacetone have extremely low rates of hepatopathy, hepatocellular carcinoma, renal disease and acute neurological crises. Those few occurrences of these complications in treated patients are likely related to nonadherence to therapy.

While NTBC has proven to be a highly effective therapy, treatment does cause significant hypertyrosinemia and resultant symptoms unless dietary restriction of phenylalanine and tyrosine is implemented concurrently with initiation of NTBC. Patients treated with NTBC are at risk for keratopathy and palmoplantar hyperkeratosis if tyrosine concentrations remain significantly elevated without intervention. A slit lamp evaluation by an ophthalmologist is indicated at the onset of any ocular symptoms, particularly photophobia, pain, or excessive lacrimation. For patients on NTBC, the goal of nutrition management is to maintain a plasma tyrosine concentration between 200 and 600 μmol/L [6]. Individuals

with plasma tyrosine levels below 600 μmol/L are extremely unlikely to have ocular or cutaneous symptoms related to hypertyrosinemia.

Long-term follow-up of patients treated with NTBC shows a reduction in full-scale intelligence quotient (FSIQ) for many treated patients as well as attentional or behavioral concerns [17–19]. Some patients have had a progressive decrease of FSIQ with time [20]. The pathogenesis of the cognitive and behavioral effects of NTBC treatment is not known for certain, but the probable role of hypertyrosinemia itself provides additional justification for close monitoring and attention to nutrition management even for those patients without any ocular or cutaneous symptoms. The neurocognitive phenotype of tyrosinemia type 3 provides additional evidence that hypertyrosinemia is likely the primary driver of the behavioral, developmental and intellectual symptoms seen in NTBC-treated patients.

Intellectual disability is not typically associated with tyrosinemia type 1 in the absence of treatment with NTBC but with the extremely high level of morbidity and mortality due to liver failure and cancer for those with untreated tyrosinemia type 1, the risk to benefit ratio favors the use of NTBC for most, if not all, patients.

The NTBC dose required by the patient may vary based on genotype, age, and other factors. NTBC therapy should be initiated as soon as possible after diagnosis of tyrosinemia type 1. Typical dosing is 1 mg/kg/day given in two daily doses [6]. NTBC has a relatively long half-life and once-daily dosing may be appropriate after the first year of life. The primary goal of NTBC treatment is to suppress succinylacetone production. If the succinylacetone concentration in blood is above the reference range, then a higher dose of NTBC should be considered. If succinylacetone concentration is normal then a lower dose of NTBC should be considered, especially if plasma tyrosine concentrations are above 600 μmol/L despite appropriate nutrition management. In addition to using succinylacetone and tyrosine concentrations to guide dosing, blood levels of NTBC itself can be measured in commercial laboratories and can provide valuable guidance. While NTBC levels of 30–70 μmol/L are recommended, the suppression of succinylacetone should be the primary determinant of dose changes [6].

There have been three reported pregnancies for women taking NTBC with plasma tyrosine concentrations of up to 800 μmol/L during pregnancy. The children born to these women have been reported to be healthy and to have typical development. NTBC is classified as a category C medication with regards to safety during pregnancy. Based on animal models, hypertyrosinemia induced by NTBC may have teratogenic effects and so close monitoring and strict attention to nutrition management is warranted during pregnancy. Given the potential risk of cessation of NTBC, there is not currently a consensus on whether or not it should be continued during pregnancy [6, 21].

13.6 Nutrition Management

Nutrition management of patients on NTBC treatment for tyrosinemia type 1 is implemented to maintain plasma tyrosine concentration within the goal range (200–600 μmol/L). Since most dietary phenylalanine is converted to tyrosine, restriction of both phenylalanine and tyrosine intake is required. For most patients, medical foods are needed to meet overall protein and energy requirements and still achieve sufficient restriction of phenylalanine and tyrosine. Medical foods with amino acid composition lacking in phenylalanine and tyrosine are commercially available from multiple manufacturers.

For infants diagnosed via newborn screening and started on NTBC therapy, a typical initial approach includes provision of intact protein via either breast milk or infant formula with the addition of medical foods to meet overall protein requirements. The relative quantity of intact protein versus medical food required by the patient is determined by frequent assessments of plasma amino acid concentrations, though typical ranges of intake at initiation of diet are 185–550 mg/day of phenylalanine and 95–275 mg/day of tyrosine [22]. Tyrosine concentrations above 600 μmol/L indicate the need to further restrict intact protein

in the diet (or decreasing the NTBC dose if possible). Conversely, plasma concentrations of phenylalanine below the reference range may indicate a need to increase the intake of intact protein or to supplement with L-phenylalanine [6].

Unlike other conditions discussed in this textbook, the patient's tolerance for intake of tyrosine and phenylalanine is not only a function of their specific gene variants and the resultant degree of residual enzyme activity. Rather, the intolerance of dietary tyrosine and phenylalanine is iatrogenic and is directly correlated with the dose of NTBC that the patient is taking. The avoidance of severe hypertyrosinemia in patients with tyrosinemia type 1 taking NTBC requires attention to both the dose of NTBC and resultant concentrations of the drug in blood as well as the dietary intake of phenylalanine and tyrosine. The patient should be prescribed the lowest effective dose of NTBC with their nutrition management adjusted accordingly.

The nutrition management of tyrosinemia type 2 and type 3 is identical to that of individuals undergoing NTBC treatment for tyrosinemia type 1.

13.7 Monitoring

Frequent monitoring of plasma amino acids, blood succinylacetone concentration and blood NTBC concentration are needed to determine the appropriate dose of NTBC, as well as dietary tyrosine and phenylalanine tolerance for the patient. Current recommendations are to assess these labs monthly for the first year of life, every 3 months until age 5 and then every 6 months after that time. Additionally, patients should have hepatic and renal function assessed with alpha-fetoprotein, coagulation studies, transaminases, electrolytes, calcium and phosphate concentrations. Patients should have annual imaging of the liver to assess for tumors [6].

13.8 Summary

Tyrosinemia type 1 is caused by a distal enzymatic block in tyrosine catabolism. The resultant accumulation of succinylacetone and other metabolites causes liver failure, liver cancer and renal tubular dysfunction. Succinylacetone also inhibits the heme synthesis pathway and causes an accumulation of toxic heme precursors that mimic acute porphyria both clinically and biochemically. The drug NTBC is a targeted inhibitor of a more proximal enzyme in tyrosine catabolism, which prevents the accumulation of succinylacetone and the resultant clinical sequela. Given the dramatic reduction in the incidence of life-limiting complications of disease, NTBC treatment is considered standard of care for patients with tyrosinemia type 1.

Administration of NTBC results in a biochemical and clinical phenocopy of tyrosinemia type 3 with severe hypertyrosinemia in the absence of dietary therapy. Severe and sustained hypertyrosinemia causes corneal and dermatological disease and likely causes developmental delay and cognitive impairment. Whether caused by type 2 tyrosinemia, type 3 tyrosinemia or by NTBC treatment, elevated tyrosine levels can be treated with reduction of dietary tyrosine and phenylalanine intake. Patients typically use medical foods in combination with reduced intake of intact protein to lower serum tyrosine levels.

Tyrosinemia type 1 is usually diagnosed via detection of succinylacetone in dried blood spots as part of newborn screening. Optimal care includes initiation of NTBC therapy early in life with regular monitoring of succinylacetone and tyrosine levels to ensure that the patient is on the lowest dose of NTBC that effectively suppresses accumulation of succinylacetone. Maintaining the lowest effective NTBC dose, in conjunction with dietary therapy, can prevent many of the manifestations of hypertyrosinemia. While patients that maintain therapeutic levels of NTBC levels are extremely unlikely to have renal and hepatic disease, ongoing monitoring for these complications is recommended.

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